Diastereoselective Synthesis of D-*erythro*- and D-*threo*-Isoxazolidinyl Nucleosides

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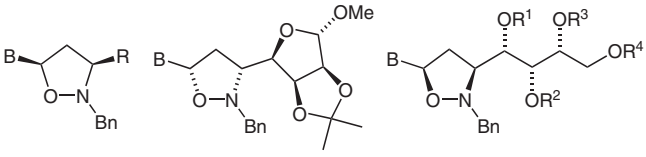
Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

Abstract: The synthesis of isoxazolidinyl nucleosides based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines **5** and **9** is reported. The 1,3-dipolar cycloaddition of D-*erythro*-nitrone **4** with vinyl acetate proceeded with respectable *anti*-facial (84:16) and *endo*-facial (72:28) diastereoselectivity to give the diastereomeric isoxazolidines **5**–**7**. The reaction of D-*threo*-nitrone **8** with vinyl acetate is more selective and proceeds with excellent *anti*-facial preference producing only two diastereomers **9** and **10**, although four diastereomers are possible. The condensation of the acetoxyisoxazolidines **5** and **9** with silylated uracil, thymine, *N*-acetylcytosine, N^2-acetylguanine, and purines proceeded with moderate to excellent stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition of silylated nucleobase is depended on the structure of the substituent at C3 originating from the starting chiral nitrone and on the attacking nucleobase.

Key words: nucleosides, isoxazolidines, cycloadditions, *C*-glycosyl nitrones, stereoselective synthesis

Nucleosides are generally defined as DNA or RNA subunits and consist of both a base moiety such as adenine, thymine, guanine, cytosine, and uracil, and a sugar moiety such as D-ribose or D-deoxyribose.[1] Many nucleoside analogues have been synthesized with modifications of the base, sugar, and phosphane region. In particular, nucleoside analogues in which the furanose ring has been replaced by different carbon or heterocyclic systems have attracted special interest by virtue of their biological action as antiviral and/or anticancer agents.[2] Among them, nucleosides **1** (B = uracil, thymine, cytosine, adenine) possessing an isoxazolidinyl moiety (carbocyclic-2′-oxo-3′-azanucleosides) are emerging as an interesting class of dideoxynucleoside analogues with potential pharmacological activity.[2] For the synthesis of modified isoxazolidinyl nucleosides **1**, two strategies can be used. In particular a one-step approach based on the 1,3-dipolar cycloaddition of nitrones to vinyl nucleobases and a two-step methodology based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines.[3] Recently, with the aim of preparing some novel azanucleosides by the transformation of modified isoxazolidinyl nucleosides **2** and **3**, we have prepared the appropriate sugar-derived nitrone possessing structures suitable for building the pyrrolidine.[4] The condensation of the acetoxyisoxazolidines prepared from D-xylose and D-lyxose with silylated uracil, thymine, cytosine, *N*-acetylcytosine, and acetylguanine proceeded with good yields and moderate to good stereoselectivity with formation of the isoxazolidinyl β- and α-nucleosides.[4c–e] The stereoselectivity of the addition was depended on the structure of the substituent at C3 in the starting chiral nitrone. We have also found that the cycloaddition of methyl acrylate with D-*erythro*-nitrones **4** and D-*threo*-nitrones **8** possessing the sterically demanding *O*-*tert*-butyldimethylsilyl group prepared from D-glucose and D-galactose, respectively, proceeds with excellent *anti*- and *endo*-facial selectivity.[5b] Continuing in our efforts to utilize chiral 1,3-dipolar cycloadditions,[4,5] we have now extended the 1,3-dipolar cycloaddition approach to the synthesis of novel 4′-aza-2′,3′-dideoxyfuranosyl nucleosides **11**–**14** by reaction of readily available chiral sugar D-erythrose and D-threose derived nitrones **4** and **8** to vinyl acetate with subsequent transformation of the thus formed 5-acetoxyisoxazolidines (Figure 1).



1 2 3

a R^1–R^2 = R^3–R^4 = CMe_2
b R^1–R^2 = CMe_2, R^3 = Bz, R^4 = TBDPS
c R^1–R^2 = CMe_2, R^3 = Bn, R^4 = TBDPS

Figure 1 Isoxazolidinyl nucleosides

D-*erythro*-Nitrone **4** reacted smoothly in refluxing vinyl acetate over 20 hours to give a 56:28:16 mixture of diastereomeric isoxazolidines **5**–**7** in 78% yield (Scheme 1). The cycloaddition proceeded with very good *anti*-facial (84:16) and *endo*-facial (72:28) diastereoselectivity and is completely regioselective with only the sterically favored 5-substituted isoxazolidines being detected. It is worthy of note that in this case the reaction, probably for steric rea-

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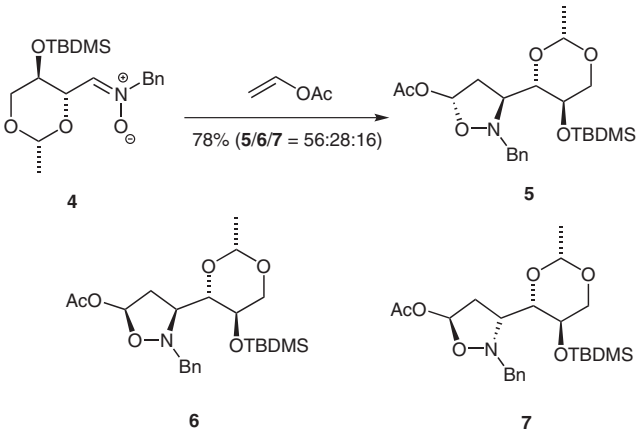
sons, proceeded with reversed diastereoselectivity as expected for an inverse demand cycloaddition reaction where the corresponding 3,5-*cis*-adducts are the major products.[3,4] Purification by HPLC provided a first fraction containing pure **6** and a second fraction containing a 93:7 mixture of isoxazolidines **5** and **6**. The major compound **5** could be isolated by crystallization from hexane. The *trans-anti* structure of **5** was established unambiguously by X-ray diffraction studies (Figure 2).[6] This allowed us to propose the structures shown in Scheme 1 for diastereomeric isoxazolidines **6** and **7**. The 3,5-*cis* relative configuration of **6** was confirmed by the observation of the NOEs in the 2D-NOESY ^{1}H NMR spectra of this compound. Such NOEs were not observed for **7**, therefore, the isolated isoxazolidine **7** possessed the *trans-syn* configuration.



Scheme 1 Cycloaddition of D-*erythro*-nitrone **4** with vinyl acetate

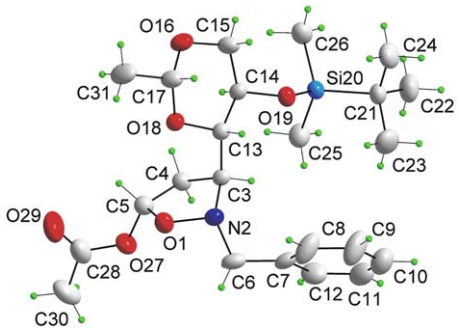
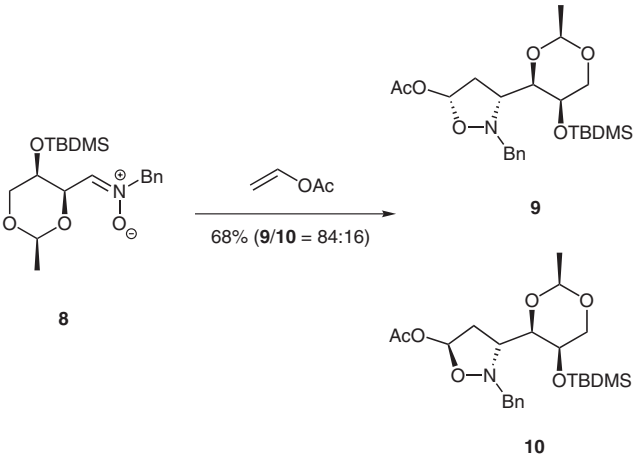


Figure 2 The molecular structure of **5**, with the numbering scheme[7] of the asymmetric unit; displacement ellipsoids are drawn at the 30% probability level

On the other hand, the reaction of D-*threo*-nitrone **8** with vinyl acetate proceeded diastereoselectively and gave only two diastereomers **9** and **10** in a 84:16 ratio with **9**, which has the *anti-cis* structure, predominating although four diastereomers are possible, showing now a preference for *exo*-attack as expected for an inverse demand cycloaddition reaction (Scheme 2).[3,4] Moreover, in this case excellent *anti*-diastereofacial induction was observed; the corresponding *syn*-adducts were not detected in the reaction mixture. Thus, the corresponding adducts **9** and **10**



Scheme 2 Cycloaddition of D-*threo*-nitrone **8** with vinyl acetate

were separated by preparative HPLC and completely characterized. The relative configuration of the cycloadducts obtained was ascertained by conventional NMR techniques including 2D NOESY, COSY, and HMBC experiments. The structure of the minor *trans-anti*-isoxazolidine **10** was established unambiguously by X-ray diffraction studies (Figure 3).[6] Based on our previous results from the 1,3-dipolar cycloaddition of sugar nitrones bearing a protected hydroxy group in the α-position[4,5] as well as the fact that 1,3-dipolar cycloaddition of electron-rich alkenes to chiral α-alkoxynitrones gave preferentially *anti*-adducts[3] and by comparison with the aforementioned results of the cycloaddition of nitrone **4** with vinyl acetate, we assigned a C1′/C3 *anti*-relationship to major isomer **9**, resulting from dipolarophile attack from the less sterically hindered *si* diastereotopic face of nitrone **8**. Thus, the observed excellent facial diastereoselectivity for the D-galactose-derived nitrone **8** is in contrast to the previously results obtained for nitrone cycloaddition to vinyl acetate.[3,4]

Next the major isoxazolidines **5** and **9** were coupled with silylated nucleobases according to the Vorbrüggen method.[8] Following extensive screening, the best reaction conditions for the Vorbrüggen nucleosidation of acetoxy-

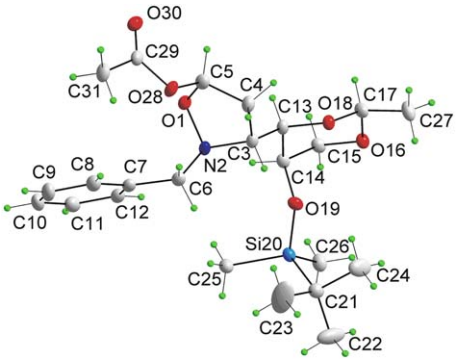


Figure 3 The molecular structure of **10**, with the numbering scheme[7] of the asymmetric unit (one molecule from two independent); displacement ellipsoids are drawn at the 30% probability level

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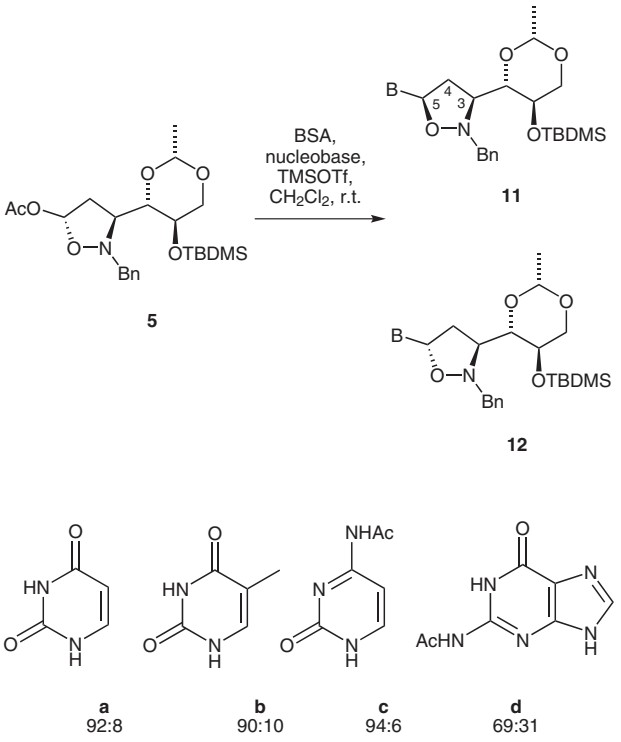
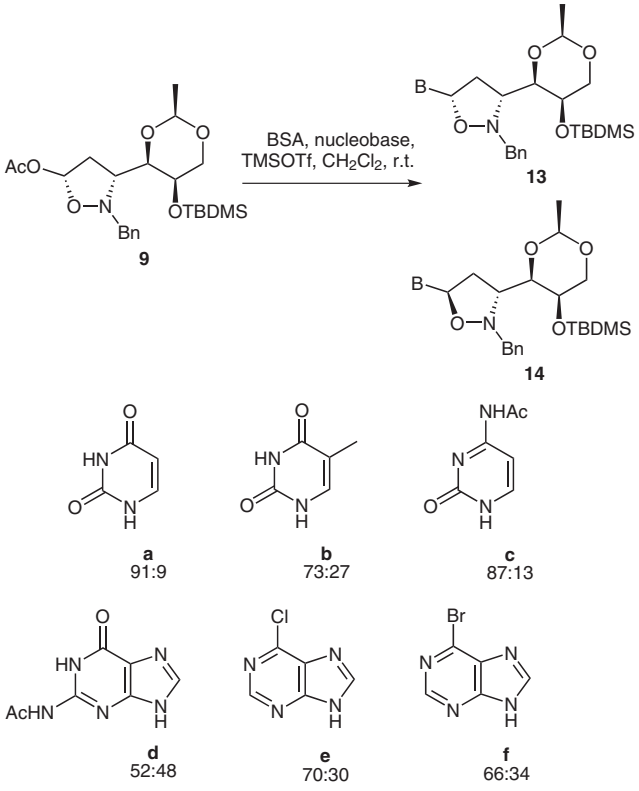
substituted isoxazolidines prepared from sugar-derived nitrones were found by us to be at room temperature in dichloromethane. The nucleosidation of *anti-trans*-isoxazolidine **5** with silylated uracil, thymine, and *N*-acetylcytosine at room temperature in dichloromethane in the presence of trimethylsilyl triflate as catalyst, afforded the β-anomeric nucleosides **11a–c** in moderate yields (65–66%), but with excellent diastereoselectivities (ratio **11a/12a** = 92:8, **11b/12b** = 90:10, **11c/12c** = 94:6; Scheme 3), whereas the reaction with N^2-acetylguanine gave a lower yield (36%) and the diastereoselectivity was only moderate (**11d/12d** = 69:31). The ratio of anomeric nucleosides was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from C4 and C5 of the isoxazolidines. Purification by flash chromatography allowed the isolation of pure nucleosides **11a–d**; their assigned stereochemistry is supported by NMR analysis. In fact, NOE measurements performed on β-anomers **11a–d** show a positive NOE effect for protons H3 when irradiating H5 thus indicating a *cis* relationship between these protons.



Scheme 3 Nucleosidation of *anti-trans*-isoxazolidine **5**

The Vorbrüggen nucleosidation of *anti-cis*-isoxazolidine **9** with silylated uracil, thymine, *N*-acetylcytosine, N^2-acetylguanine, and 6-chloro- and 6-bromopurine at room temperature in dichloromethane in the presence of trimethylsilyl triflate as catalyst, proceeded with low (purines) to good (uracil, thymine, and *N*-acetylcytosine) yields and from moderate to good stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides **13** and **14** (ratio **13a/14a** = 91:9, **13b/14b** = 73:27, **13c/14c** = 87:13, **13d/14d** = 52:48, **13e/14e** = 70:30, **13f/14f** = 66:34, Scheme 4). For uracil and *N*-acetylcytosine, the β-anomers **13** clearly predominate, while in the case of N^2-acetylguanine and purines a significant amount of α-anomer **14** was obtained. This lower diastereoselectivity is in contrast with the excellent diastereoselectivity observed for **5**, but these results are fully in accord with the data obtained for the related Vorbrüggen nucleosidations.[3,4,9] Purification by flash chromatography allowed the isolation not only of all β-nucleosides **13a–f**, but also the three α-nucleosides **14b**,**e**,**f** were obtained. The assigned configuration is supported by NMR analysis.



Scheme 4 Nucleosidation of *anti-cis*-isoxazolidine **9**

In conclusion, the synthesis of isoxazolidinyl nucleosides, as potential antiviral agents, based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines **5** and **9** is reported. The 1,3-dipolar cycloaddition of D-*erythro*-nitrone **4** with vinyl acetate proceeded with respectable *anti*-facial (84:16) and *endo*-facial (72:28) diastereoselectivity to give the diastereomeric isoxazolidines **5–7**. The reaction of D-*threo*-nitrone **8** to vinyl acetate is more selective and proceeds with an excellent *anti*-facial preference producing only two diastereomers **9** and **10**, although four diastereomers are possible. The condensation of the acetoxyisoxazolidines **5** and **9** with silylated uracil, thymine, *N*-acetylcytosine, N^2-acetylguanine, and purines proceeded with moderate to excellent stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition of silylated nucleobase, is depended on the structure of the substituent at C3 originated from the starting chiral nitrone and on the attacking nucleobase.

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All commercially available starting materials and reagents (Fluka, Merck, Across or Aldrich) were used without further purification. Solvents were dried before use. TLC (Alugram Sil G/UV_{254} Macherey-Nagel) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040–0.063 mm, Merck). The ^1H and ^{13}C NMR spectra of $CDCl_3$ solns were obtained using Varian Inova-600 (600 MHz), VXR-300 (300 MHz) and Bruker AC 500 (500 MHz) instruments; TMS was the internal reference. Specific rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the Na D line (589 nm) using a 1 dm cell. HPLC analyses were performed on preparative column (diameter 32, length 237 mm) with nucleosil 50-5. Elemental analyses were conducted using the Fisons EA 1108 Analysator. Nitrones **4** and **8** were prepared from the corresponding aldehydes by the reaction with *N*-benzylhydroxylamine according to the procedure already described.[5a,b]

1,3-Dipolar Cycloaddition of D-*erythro*-Nitrone 4 with Vinyl Acetate; General Procedure

A mixture of the nitrone **4** (1.040 g, 2.85 mmol) and vinyl acetate (25 mL) was stirred for 24 h under reflux. When starting nitrone had been consumed (TLC), solvent was evaporated under vacuum to give a 56:28:16 mixture of diastereomeric isoxazolidines **5**–**7** in 78% yield. The mixture of diastereomers was separated by preparative HPLC (hexane–EtOAc, 85:15).

(3*S*,5*S*)-5-Acetoxy-2-benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (5)
Colorless solid; yield: 525 mg (41%); mp 91–93 °C.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H, C_6H_5), 6.35 (d, *J* = 4.9 Hz, 1 H, H5), 4.63 (q, *J* = 4.9 Hz, 1 H, H2′), 4.27 (d, *J* = 12.9 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 4.09 (d, *J* = 13.2 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 3.96 (dd, *J* = 4.4, 10.7 Hz, 1 H, H4b′), 3.64 (dd, *J* = 7.7 Hz, 1 H, H3), 3.39 (m, 2 H, H6′, H5′), 3.27 (m, 1 H, H4a′), 2.84 (ddd, *J* = 5.2, 8.2, 13.4 Hz, 1 H, H4b), 2.32 (ddd, *J* = 1.4, 7.1, 12.9 Hz, 1 H, H4a), 2.05 (s, 3 H, COCH_3), 1.32 (d, *J* = 4.9 Hz, 3 H, CH_3), 0.82 [s, 9 H, OSiC(CH_3)$_3$], 0.03, 0.02 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 169.9 (CO), 136.6, 129.4, 128.3, 127.5 (C_6H_5), 98.8 (C2′), 98.3 (C5), 80.6 (C6′), 71.1 (C4′), 64.3 (NCH$_2$Ph), 64.2 (C5′), 62.4 (C3), 35.4 (C4), 25.8 [OSiC(*C*H$_3$)$_3$], 21.3 (CO*C*H$_3$), 20.4 (CH*C*H$_3$), 17.7 [OSi*C*(CH$_3$)$_3$], –4.3, –5.0 [OSi(CH$_3$)$_2$].

Anal. Calcd for $C_{23}H_{37}NO_6Si$ (451.6): C, 61.17; H, 8.26; N, 3.10. Found: C, 61.62; H, 8.27; N, 2.95.

(3*S*,5*R*)-5-Acetoxy-2-benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (6)
Colorless solid; yield: 249 mg (19%); mp 112–114 °C.

[α]$_D$ –21.3 (*c* 0.15, CH_2Cl_2).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H, C_6H_5), 6.28 (d, *J* = 4.1 Hz, 1 H, H5), 4.68 (q, *J* = 5.1 Hz, 1 H, H2′), 4.27 (d, *J* = 13.7 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 4.10 (d, *J* = 13.7 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 4.07 (dd, *J* = 5.2, 11.0 Hz, 1 H, H4b′), 3.78 (ddd, *J* = 5.1, 8.5, 9.8 Hz, 1 H, H5′), 3.47 (m, 2 H, H6′, H3), 3.37 (dd, *J* = 10.4 Hz, 1 H, H4a′), 2.52 (m, 2 H, H4a,b), 2.05 (s, 3 H, COCH_3), 1.34 (d, *J* = 4.9 Hz, 3 H, CH_3,), 0.88 [s, 9 H, OSiC(CH_3)$_3$], 0.10, 0.09 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 169.9 (CO), 137.7, 129.4, 128.2, 127.2 (C_6H_5), 98.8 (C2′), 97.6 (C5), 84.0 (C6′), 71.1 (C4′), 65.7 (NCH$_2$C$_6$H$_5$), 65.3 (C5′), 64.0 (C3), 39.8 (C4), 25.8 [OSiC(*C*H$_3$)$_3$], 21.4 (CO*C*H$_3$), 20.4 (CH*C*H$_3$), 17.9 [OSi*C*(CH$_3$)$_3$], –3.7, –4.5 [OSi(CH$_3$)$_2$].

Anal. Calcd for $C_{23}H_{37}NO_6Si$ (451.6): C, 61.17; H, 8.26; N 3.10. Found: C, 61.46; H, 8.24; N 3.00.

(3*R*,5*R*)-5-Acetoxy-2-benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (7)
Colorless solid; yield: 227 mg (18%); mp 77–79 °C.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 5 H, C_6H_5), 6.28 (dd, *J* = 2.5, 6.6 Hz, 1 H, H5), 4.62 (q, *J* = 4.9 Hz, 1 H, H2′), 4.23 (d, *J* = 14.3 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 4.00 (m, 1 H, H4b′), 3.98 (d, *J* = 14.3 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 3.41 (m, 2 H, H6′, H5′), 3.29 (m, 1 H, H4a′), 3.24 (m, 1 H, H3), 2.72 (ddd, *J* = 2.6, 8.8, 13.2 Hz, 1 H, H4b), 2.52 (ddd, *J* = 6.8, 9.1, 13.5 Hz, 1 H, H4a), 2.07 (s, 3 H, COCH_3), 1.36 (d, *J* = 4.9 Hz, 3 H, CH_3,), 0.87 [s, 9 H, OSiC(CH_3)$_3$], 0.05, 0.03 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 170.8 (CO), 135.7, 129.8, 128.1, 127.4 (C_6H_5), 98.8 (C2′), 95.3 (C5), 77.9 (C6′), 71.3 (C4′), 64.5 (C5′), 63.9 (C3), 60.7 (NCH$_2$C$_6$H$_5$), 36.1 (C4), 25.6 [OSiC(*C*H$_3$)$_3$], 21.3 (CO*C*H$_3$), 20.4 (CH*C*H$_3$), 17.8 [OSi*C*(CH$_3$)$_3$], –4.2, –4.8 [OSi(CH$_3$)$_2$].

Anal. Calcd for $C_{23}H_{37}NO_6Si$ (451.6): C, 61.17; H, 8.26; N, 3.10. Found: C, 61.20; H, 8.26; N 2.86.

1,3-Dipolar Cycloaddition of D-*threo*-Nitrone 8 with Vinyl Acetate

A mixture of the nitrone **8** (1.706 g, 4.67 mmol) and vinyl acetate (25 mL) was stirred for 24 h under reflux. When starting nitrone had been consumed (TLC), solvent was evaporated under vacuum to give 84:16 mixture of diastereomeric isoxazolidines **9** and **10** in 68% yield. The mixture of diastereomers was separated by preparative HPLC (hexane–EtOAc, 88:12).

(3*R*,5*S*)-5-Acetoxy-2-benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (9)
Colorless oil; yield: 1.254g (59%).

[α]$_D$ +81.3 (*c* 0.16, CH_2Cl_2).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H, C_6H_5), 6.41 (d, *J* = 5.8 Hz, 1 H, H5), 4.72 (q, *J* = 5.1 Hz, 1 H, H2′), 4.11 (m, 1 H, H4b′), 4.08 (d, *J* = 14.1 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 3.94 (m, 1 H, H5′), 3.90 (d, *J* = 14.1 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 3.76 (m, 1 H, H4a′), 3.71 (m, 1 H, H6′), 3.63 (m, 1 H, H3), 2.54 (dd, *J* = 1.3, 14.1 Hz, 1 H, H4b), 2.25 (ddd, *J* = 6.1, 8.1, 14.1 Hz, 1 H, H4a), 2.01 (s, 3 H, COCH_3), 1.36 (d, *J* = 4.5 Hz, 3 H, CH_3), 0.96 [s, 9 H, OSiC(CH_3)$_3$], 0.17, 0.11 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 169.8 (CO), 136.5, 129.3, 128.4, 127.6 (C_6H_5), 99.1 (C2′), 97.2 (C5), 78.7 (C6′), 71.3 (C4′), 64.6 (C5′), 63.1 (NCH$_2$C$_6$H$_5$), 62.2 (C3), 35.8 (C4), 26.0 [OSiC(*C*H$_3$)$_3$], 21.3 (CO*C*H$_3$), 21.0 (CH*C*H$_3$), 18.4 [OSi*C*(CH$_3$)$_3$], –3.8, –3.9 [OSi(CH$_3$)$_2$].

Anal. Calcd for $C_{23}H_{37}NO_6Si$ (451.6): C, 61.17; H, 8.26; N, 3.10. Found: C, 61.70; H, 8.27; N 3.02.

(3*R*,5*R*)-5-Acetoxy-2-benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (10)
Colorless solid; yield: 189 mg (9%); mp 59–60 °C.

[α]$_D$ –23 (*c* 0.10, CH_2Cl_2).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, C_6H_5), 6.40 (dd, *J* = 2.6, 6.4 Hz, 1 H, H5), 4.70 (q, *J* = 5.1 Hz, 1 H, H2′), 4.30 (d, *J* = 13.5 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 4.06 (dd, *J* = 1.8, 12.3 Hz, 1 H, H4b′), 3.99 (d, *J* = 13.5 Hz, 1 H, NC*H*$_2$C$_6$H$_5$), 3.87 (m, 1 H, H5′), 3.75 (m, 1 H, H3), 3.72 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.41 (dd, *J* = 1.3, 9.0 Hz, 1 H, H6′), 2.87 (ddd, *J* = 3.9, 6.4, 10.3 Hz, 1 H, H4b), 2.62 (ddd, *J* = 2.6, 7.7, 10.3 Hz, 1 H, H4a), 2.08 (s, 3 H, COCH_3), 1.35 (d, *J* = 5.1 Hz, 3 H, CH_3,), 0.93 [s, 9 H, OSiC(CH_3)$_3$], 0.15, 0.08 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 169.7 (CO), 137.3, 128.6, 128.2, 127.2 (C_6H_5), 99.1 (C2′), 98.9 (C5), 79.5 (C6′), 71.1 (C4′),

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64.6 (C5′), 63.7 (C3), 63.3 ($NCH_2C_6H_5$), 37.2 (C4), 25.8 [OSiC(CH_3)$_3$], 21.2 (COCH_3), 20.8 (CHCH_3), 18.2 [OSiC(CH_3)$_3$], –4.0, –4.2 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{23}H_{37}NO_6Si$ (451.6): C, 61.17; H, 8.26; N, 3.10. Found: C, 61.44 H, 8.22; N 2.97.

Nucleosidation of Acetoxyisoxazolidines; General Procedure

A suspension of the corresponding nucleobase (0.58 mmol) in anhyd CH_2Cl_2 (3 mL) was treated with *N*,*O*-bis(trimethylsilyl)acetamide (2.32 mmol) and stirred for 20 min at reflux. Isoxazolidine **5** or **9** (0.48 mmol) in anhyd CH_2Cl_2 (3 mL) and TMSOTf (0.72 mmol) were added to the obtained clear soln. The mixture was stirred at r.t. for 2 h. The soln was neutralized by addition of 5% aq $NaHCO_3$. The organic phase was separated, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by column chromatography (silica gel).

1-{(3*S*,5*R*)-2-Benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}pyrimidine-2,4(1*H*,3*H*)-dione (11a)

According to the general procedure, the mixture from isoxazolidine **5** (0.34 mmol) and uracil (0.41 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **11a** (0.112 g, 65%) as a colorless solid; mp 71–73 °C.

$[\alpha]_D$ –107 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.05 (br s, 1 H, NH), 8.10 (d, *J* = 8.2 Hz, 1 H, H6″), 7.34–7.28 (m, 5 H, C_6H_5), 6.27 (dd, *J* = 2.6, 7.9 Hz, 1 H, H5), 5.60 (dd, *J* = 1.8, 8.2 Hz, 1 H, H5″), 4.62 (q, *J* = 5.0 Hz, 1 H, H2′), 4.16 (d, *J* = 13.5 Hz, 1 H, NC$H_2C_6H_5$), 3.99 (m, 1 H, H4a′), 3.98 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 3.37 (m, 3 H, H5′, H6′, H3), 3.28 (m, 1 H, H4b′), 2.80 (ddd, *J* = 7.6, 10.0, 13.5 Hz, 1 H, H4a), 2.70 (ddd, *J* = 2.9, 7.2, 13.5 Hz, 1 H, H4b), 1.26 (d, *J* = 4.7 Hz, 3 H, CH_3), 0.87 [s, 9 H, OSiC(CH_3)$_3$], 0.06, 0.05 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 163.6 (CO), 150.7 (CO), 142.3 (C6″), 136.1–127.7 (C_6H_5), 101.0 (C5″), 98.5 (C2′), 82.8 (C5), 78.7 (C6′), 71.1 (C4′), 64.2 (C3), 64.1 (C5′), 61.2 ($NCH_2C_6H_5$), 36.0 (C4), 25.6 [OSiC(CH_3)$_3$], 20.2 (CHCH_3), 17.7 [OSiC(CH_3)$_3$], –4.2, –5.0 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{25}H_{37}N_3O_6Si$ (503.7): C, 59.62; H, 7.40; N, 8.34. Found: C, 59.34; H, 7.62; N, 7.97.

1-{(3*S*,5*R*)-2-Benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (11b)

According to the general procedure, the mixture from isoxazolidine **5** (0.40 mmol) and thymine (0.48 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **11b** (0.145 g, 51%) as a colorless solid; mp 188–189 °C.

$[\alpha]_D$ –93.6 (*c* 0.11, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.03 (br s, 1 H, NH), 7.90 (s, 1 H, H6″), 7.35–7.28 (m, 5 H, C_6H_5), 6.28 (dd, *J* = 3.2, 7.9 Hz, 1 H, H5), 4.64 (q, *J* = 5.0 Hz, 1 H, H2′), 4.18 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.01 (dd, *J* = 4.1, 11.1 Hz, 1 H, H4a′), 3.97 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 3.41 (m, 2 H, H5′, H6′), 3.35 (m, 1 H, H3), 3.30 (m, 1 H, H4b′), 2.79 (ddd, *J* = 7.6, 9.4, 13.5 Hz, 1 H, H4a), 2.70 (ddd, *J* = 3.5, 7.6, 13.5 Hz, 1 H, H4b), 1.88 (s, 3 H, CH_3), 1.29 (d, *J* = 4.7 Hz, 3 H, CH_3,), 0.87 [s, 9 H, OSiC(CH_3)$_3$], 0.06, 0.05 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 164.0 (CO), 150.7 (CO), 137.9 (C6″), 136.3–127.6 (C_6H_5), 109.5 (C5″), 98.6 (C2′), 82.4 (C5), 78.8 (C6′), 71.2 (C4′), 64.3 (C3), 64.2 (C5′), 60.9 ($NCH_2C_6H_5$), 35.9 (C4), 25.6 [OSiC(CH_3)$_3$], 20.4 (CHCH_3), 17.7 [OSiC(CH_3)$_3$], 12.4 (CH_3), –4.1, –5.0 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{26}H_{39}N_3O_6Si$ (517.7): C, 60.32; H, 7.59; N, 8.12. Found: C, 60.02; H, 7.66; N, 7.72.

4-(Acetylamino)-1-{(3*S*,5*R*)-2-benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}pyrimidin-2(1*H*)-one (11c)

According to the general procedure, the mixture from isoxazolidine **5** (0.22 mmol) and *N*-acetylcytosine (0.27 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 15:85) to give **11c** (0.080 g, 66%) as a colorless solid; mp 49–50 °C.

$[\alpha]_D$ –28.75 (*c* 0.08, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.12 (br s, 1 H, NH), 8.21 (d, *J* = 7.3 Hz, 1 H, H6″), 7.37–7.28 (m, 5 H, C_6H_5), 7.32 (d, *J* = 7.3 Hz, 1 H, H5″), 6.16 (dd, *J* = 2.2, 7.3 Hz, 1 H, H5), 4.57 (q, *J* = 4.9 Hz, 1 H, H2′), 4.19 (d, *J* = 13.2 Hz, 1 H, NC$H_2C_6H_5$), 3.99 (d, *J* = 13.9 Hz, 1 H, NC$H_2C_6H_5$), 3.96 (dd, *J* = 4.8, 9.9 Hz, 1 H, H4a′), 3.37 (m, 3 H, H5′, H6′, H3), 3.26 (m, 1 H, H4b′), 2.89 (ddd, *J* = 7.3, 9.9, 13.6 Hz, 1 H, H4a), 2.72 (ddd, *J* = 2.2, 6.6, 13.6 Hz, 1 H, H4b), 2.25 (s, 3 H, $COCH_3$), 1.13 (d, *J* = 5.1 Hz, 3 H, CH_3,), 0.87 [s, 9 H, OSiC(CH_3)$_3$], 0.06, 0.04 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 171.0 (CO), 162.5 (C4″), 155.4 (CO), 146.6 (C6″), 136.2–127.8 (C_6H_5), 98.5 (C2′), 95.5 (C5″), 85.1 (C5), 78.7 (C6′), 71.1 (C4′), 64.2 (C5′), 64.1 (C3), 61.6 ($NCH_2C_6H_5$), 36.8 (C4), 25.6 [OSiC(CH_3)$_3$], 24.8 ($COCH_3$), 20.1 (CHCH_3), 17.7 [OSiC(CH_3)$_3$], –4.2, –5.0 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{27}H_{40}N_4O_6Si$ (544.7): C, 59.53; H, 7.40; N, 10.29. Found: C, 59.49; H, 7.74; N, 9.98.

***N*^{2}-(Acetylamino)-1-{(3*S*,5*R*)-2-benzyl-3-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}guanine (11d)**

According to the general procedure, the mixture from isoxazolidine **5** (0.18 mmol) and *N*^{2}-acetylguanine (0.22 mmol) was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 97:3) to give **11d** (0.032 g, 30%) as a colorless solid; mp 173–175 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.31 (br s, 1 H, CONH), 11.22 (br s, 1 H, NHAc), 8.57 (s, 1 H, H8″), 7.40–7.26 (m, 5 H, C_6H_5), 6.83 (dd, *J* = 2.9, 6.6 Hz, 1 H, H5), 4.60 (q, *J* = 4.8 Hz, 1 H, H2′), 4.22 (d, *J* = 14.7 Hz, 1 H, NC$H_2C_6H_5$), 4.02 (d, *J* = 13.9 Hz, 1 H, NC$H_2C_6H_5$), 3.98 (m, 1 H, H4a′), 3.33 (m, 4 H, H5′, H6′, H3, H4b′), 2.94 (m, 2 H, H4a,b), 2.37 (s, 3 H, $COCH_3$), 1.23 (d, *J* = 5.1 Hz, 3 H, CH_3), 0.89 [s, 9 H, OSiC(CH_3)$_3$], 0.08, 0.05 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 173.1 (CO), 156.2, 153.3, 147.8, 143.3 ($C_{adenine}$), 136.3–127.5 (C_6H_5), 111.2 ($C_{adenine}$), 98.6 (C2′), 83.1 (C5), 78.5 (C6′), 71.2 (C4′), 64.5 (C3), 64.2 (C5′), 60.7 ($NCH_2C_6H_5$), 37.3 (C4), 25.6 [OSiC(CH_3)$_3$], 24.6 ($COCH_3$), 20.2 (CHCH_3), 17.8 [OSiC(CH_3)$_3$], –4.1, –4.9 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{28}H_{40}N_6O_6Si$ (584.7): C, 57.51; H, 6.89; N, 14.37. Found: C, 57.47; H, 7.28; N, 14.10.

1-{(3*R*,5*S*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}pyrimidine-2,4(1*H*,3*H*)-dione (13a)

According to the general procedure, the mixture from isoxazolidine **9** (0.55 mmol) and uracil (0.67 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **13a** (0.187 g, 67%) as a colorless solid; mp 44–45 °C.

$[\alpha]_D$ +84 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.03 (br s, 1 H, NH), 8.06 (d, *J* = 8.2 Hz, 1 H, H6″), 7.33–7.31 (m, 5 H, C_6H_5), 6.31 (dd, *J* = 3.5, 7.0 Hz, 1 H, H5), 5.63 (d, *J* = 8.2 Hz, 1 H, H5″), 4.68 (q, *J* = 5.0 Hz, 1 H, H2′), 4.13 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.01 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 3.98 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.72

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(dd, *J* = 1.2, 12.3 Hz, 1 H, H4b′), 3.60 (m, 1 H, H5′), 3.52 (m, 1 H, H6′), 3.11 (m, 1 H, H3), 2.94–2.80 (m, 2 H, H4a,b), 1.30 (d, *J* = 4.7 Hz, 3 H, CH_3), 0.92 [s, 9 H, $OSiC(CH_3)_3$], 0.10, 0.08 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 163.9 (CO), 150.8 (CO), 141.9 (C6″), 136.2, 128.5, 128.3, 127.5 (C_6H_5), 101.0 (C5″), 98.6 (C2′), 82.8 (C5), 77.6 (C6′), 71.3 (C4′), 66.6 (C3), 65.8 (C5′), 61.6 ($NCH_2C_6H_5$), 37.1 (C4), 25.7 [$OSiC(CH_3)_3$], 20.6 ($CHCH_3$), 18.0 [$OSiC(CH_3)_3$], –4.4, –4.6 [$OSi(CH_3)_2$].

Anal. Calcd for $C_{25}H_{37}N_3O_6Si$ (503.7): C, 59.62; H, 7.40; N, 8.34. Found: C, 59.40; H, 7.71; N 7.89.

1-{(3*R*,5*S*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (13b) and 1-{(3*R*,5*R*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (14b)

According to the general procedure, the mixture from isoxazolidine **9** (0.55 mmol) and thymine (0.067 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **13b** (0.145 g, 51%) as a colorless solid; mp 62–63 °C and **14b** (0.066 g, 23%) as a colorless solid; mp 152–153 °C.

13b

$[\alpha]_D$ +85 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.75 (br s, 1 H, NH), 7.76 (d, *J* = 1.2 Hz, 1 H, H6″), 7.34–7.28 (m, 5 H, C_6H_5), 6.32 (dd, *J* = 3.5, 7.6 Hz, 1 H, H5), 4.70 (q, *J* = 5.0 Hz, 1 H, H2′), 4.13 (d, *J* = 14.1 Hz, 1 H, $NCH_2C_6H_5$), 4.00 (d, *J* = 14.1 Hz, 1 H, $NCH_2C_6H_5$), 3.98 (m, 1 H, H4a′), 3.75 (m, 1 H, H4b′), 3.63 (m, 1 H, H5′), 3.56 (m, 1 H, H6′), 3.14 (ddd, *J* = 3.5, 6.7, 9.4 Hz, 1 H, H3), 2.94–2.75 (m, 2 H, H4a,b), 1.89 (d, *J* = 1.2 Hz, 3 H, CH_3), 1.34 (d, *J* = 5.3 Hz, 3 H, CH_3), 0.93 [s, 9 H, $OSiC(CH_3)_3$], 0.11, 0.08 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 164.2 (CO), 150.9 (CO), 137.3 (C6″), 136.5, 128.5, 128.3, 127.5 (C_6H_5), 109.6 (C5″), 98.8 (C2′), 82.5 (C5), 77.9 (C6′), 71.4 (C4′), 66.5 (C3), 65.8 (C5′), 61.3 ($NCH_2C_6H_5$), 37.0 (C4), 25.8 [$OSiC(CH_3)_3$], 20.8 ($CHCH_3$), 18.0 [$OSiC(CH_3)_3$], 12.4 (CH_3), –4.3, –4.4 [$OSi(CH_3)_2$].

Anal. Calcd for $C_{26}H_{39}N_3O_6Si$ (517.7): C, 60.32; H, 7.59; N, 8.12. Found: C, 59.85; H, 7.59; N, 7.79.

14b

$[\alpha]_D$ +34.5 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.37 (br s, 1 H, NH), 7.40–7.30 (m, 5 H, C_6H_5), 7.06 (d, *J* = 1.2 Hz, 1 H, H6″), 5.98 (dd, *J* = 6.8, 6.7 Hz, 1 H, H5), 4.77 (q, *J* = 5.0 Hz, 1 H, H2′), 4.16 (d, *J* = 14.6 Hz, 1 H, $NCH_2C_6H_5$), 4.08 (dd, *J* = 1.6, 12.1 Hz, 1 H, H4a′), 4.07 (d, *J* = 14.6 Hz, 1 H, $NCH_2C_6H_5$), 3.85 (m, 1 H, H5′), 3.80 (dd, *J* = 1.2, 12.4 Hz, 1 H, H4b′), 3.70 (m, 2 H, H6′, H3), 3.28 (ddd, *J* = 2.4, 7.1, 14.0 Hz, 1 H, H4a), 2.47 (m, 1 H, H4b), 1.76 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.38 (d, *J* = 5.0 Hz, 3 H, CH_3), 0.92 [s, 9 H, $OSiC(CH_3)_3$], 0.14, 0.05 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 164.0 (CO), 150.3 (CO), 136.4 (C6″), 135.6, 128.6, 128.3, 127.7 (C_6H_5), 110.1 (C5″), 99.1 (C2′), 86.5 (C5), 77.5 (C6′), 71.3 (C4′), 64.9 (C5′), 64.8 (C3), 61.4 ($NCH_2C_6H_5$), 36.6 (C4), 25.8 [$OSiC(CH_3)_3$], 20.8 ($CHCH_3$), 18.2 [$OSiC(CH_3)_3$], 12.3 (CH_3), –4.1, –4.3 [$OSi(CH_3)_2$].

Anal. Calcd for $C_{26}H_{39}N_3O_6Si$ (517.7): C, 60.32; H, 7.59; N, 8.12. Found: C, 59.99; H, 7.75; N, 8.31.

4-(Acetylamino)-1-{(3*R*,5*S*)-2-benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}pyrimidin-2-one (13c) and 4-(Acetylamino)-1-{(3*R*,5*R*)-2-benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}pyrimidin-2-one (14c)

According to the general procedure, the mixture from isoxazolidine **9** (0.43 mmol) and *N*-acetylcytosine (0.53 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 20:80) to give **13c** (0.150 g, 50%) as a colorless solid; mp 79–80 °C and **14c** (0.028 g, 9%) as a colorless solid; mp 219–220 °C.

13c

$[\alpha]_D$ +18 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.25 (br s, 1 H, NH), 8.14 (d, *J* = 7.0 Hz, 1 H, H6″), 7.37–7.29 (m, 5 H, C_6H_5), 7.32 (d, *J* = 7.0 Hz, 1 H, H5″), 6.18 (dd, *J* = 1.8, 7.0 Hz, 1 H, H5), 4.61 (q, *J* = 4.9 Hz, 1 H, H2′), 4.17 (d, *J* = 14.1 Hz, 1 H, $NCH_2C_6H_5$), 4.04 (d, *J* = 13.5 Hz, 1 H, $NCH_2C_6H_5$), 3.98 (dd, *J* = 1.2, 12.6 Hz, 1 H, H4a′), 3.69 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.53 (m, 1 H, H5′), 3.42 (dd, *J* = 1.2, 4.1 Hz, 1 H, H6′), 3.22 (m, 1 H, H3), 2.99 (ddd, *J* = 7.6, 10.0, 14.7 Hz, 1 H, H4a), 2.82 (ddd, *J* = 1.8, 5.3, 14.7 Hz, 1 H, H4b), 2.25 (s, 3 H, $COCH_3$), 1.20 (d, *J* = 5.3 Hz, 3 H, CH_3), 0.92 [s, 9 H, $OSiC(CH_3)_3$], 0.11, 0.08 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 171.1 (CO), 162.8 (C4″), 155.2 (CO), 146.0 (C6″), 136.5, 128.7, 128.6, 127.8 (C_6H_5), 98.9 (C2′), 95.5 (C5″), 85.4 (C5), 78.7 (C6′), 71.3 (C4′), 65.9 (C5′), 65.7 (C3), 62.5 ($NCH_2C_6H_5$), 38.8 (C4), 25.9 [$OSiC(CH_3)_3$], 24.8 ($COCH_3$), 20.6 ($CHCH_3$), 18.2 [$OSiC(CH_3)_3$], –4.2 [$OSi(CH_3)_2$].

Anal. Calcd for $C_{27}H_{40}N_4O_6Si$ (544.7): C, 59.53; H, 7.40; N, 10.29. Found: C, 59.10; H, 7.79; N, 9.83.

14c

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.00 (br s, 1 H, NH), 7.68 (d, *J* = 7.6 Hz, 1 H, H6″), 7.42–7.31 (m, 5 H, C_6H_5), 7.26 (d, *J* = 7.6 Hz, 1 H, H5″), 5.94 (dd, *J* = 6.3, 6.4 Hz, 1 H, H5), 4.76 (q, *J* = 5.1 Hz, 1 H, H2′), 4.13 (d, *J* = 14.1 Hz, 1 H, $NCH_2C_6H_5$), 4.03 (m, 2 H, $NCH_2C_6H_5$, H4a′), 3.90 (m, 1 H, H5′), 3.80 (m, 1 H, H4a′), 3.71 (m, 1 H, H6′, H3), 3.56 (ddd, *J* = 1.8, 7.0, 14.4 Hz, 1 H, H4a), 2.50 (m, 1 H, H4b), 2.26 (s, 3 H, $COCH_3$), 1.37 (d, *J* = 4.7 Hz, 3 H, CH_3), 0.90 [s, 9 H, $OSiC(CH_3)_3$], 0.13, 0.02 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 171.0 (CO), 162.9 (C4″), 155.1 (CO), 144.1 (C6″), 136.4, 128.7, 128.0, 127.9 (C_6H_5), 99.2 (C2′), 95.9 (C5″), 89.0 (C5), 77.6 (C6′), 71.3 (C4′), 64.8 (C5′), 64.6 (C3), 61.7 ($NCH_2C_6H_5$), 37.7 (C4), 25.8 [$OSiC(CH_3)_3$], 24.8 ($COCH_3$), 20.9 ($CHCH_3$), 18.2 [$OSiC(CH_3)_3$], –4.1, –4.3 [$OSi(CH_3)_2$].

Anal. Calcd for $C_{27}H_{40}N_4O_6Si$ (544.7): C, 59.53; H, 7.40; N, 10.29. Found: C, 59.22; H, 7.66; N, 10.57.

***N*^{2}-Acetyl-1-{(3*R*,5*S*)-2-benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}guanine (13d)**

According to the general procedure, the mixture from isoxazolidine **9** (0.66 mmol) and *N*^{2}-acetylguanine (0.80 mmol) was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 97:3) to give **13d** (0.118 g, 31%) as a colorless solid; mp 117–118 °C.

$[\alpha]_D$ +106.2 (*c* 0.08, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.36 (br s, 1 H, CONH), 11.56 (br s, 1 H, NHAc), 8.53 (s, 1 H, H8″), 7.31–7.25 (m, 5 H, C_6H_5), 6.83 (dd, *J* = 1.2, 8.2 Hz, 1 H, H5), 4.65 (q, *J* = 5.0 Hz, 1 H, H2′), 4.15 (d, *J* = 14.7 Hz, 1 H, $NCH_2C_6H_5$), 4.08 (d, *J* = 14.1 Hz, 1 H, $NCH_2C_6H_5$), 3.98 (d, *J* = 12.3 Hz, 1 H, H4a′), 3.71 (d, *J* = 12.3 Hz, 1 H, H4b′), 3.59 (m, 1 H, H5′), 3.55 (m, 1 H, H6′), 3.16 (m, 1 H, H3), 3.09 (ddd, *J* = 1.5, 5.6, 13.2 Hz, 1 H, H4a), 3.01 (m, 1 H, H4b), 2.17 (d, *J* = 1.2 Hz, 3 H, $COCH_3$), 1.30 (d, *J* = 5.3 Hz, 3 H, CH_3), 0.92 [s, 9 H, $OSiC(CH_3)_3$], 0.11, 0.09 [2 × s, 2 × 3 H, $OSi(CH_3)_2$].

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^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 173.2 (CO), 156.4, 153.2, 147.9, 142.8 ($C_{adenine}$), 136.4–127.6 (C_6H_5), 111.4 ($C_{adenine}$), 98.8 (C2′), 83.5 (C5), 77.7 (C6′), 71.5 (C4′), 66.8 (C3), 65.9 (C5′), 61.3 ($NCH_2C_6H_5$), 38.3 (C4), 25.8 [OSiC(CH_3)$_3$], 24.5 ($COCH_3$), 20.7 (CHCH_3), 18.1 [OSiC(CH_3)$_3$], –4.3, –4.4 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{28}H_{40}N_6O_6Si$ (584.7): C, 57.51; H, 6.89; N, 14.37. Found: C, 57.61; H, 7.12; N, 14.04.

1-{(3*R*,5*S*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-chloropurine (13e) and 1-{(3*R*,5*R*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-chloropurine (14e)

According to the general procedure, the mixture from isoxazolidine **9** (0.66 mmol) and 6-chloropurine (0.18 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **13e** (0.100 g, 28%) as a colorless oil and **14e** (0.046 g, 13%) as a colorless oil.

13e

$[\alpha]_D$ +103 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.97 (s, 1 H, H2″), 8.71 (s, 1 H, H8″), 7.30–7.25 (m, 5 H, C_6H_5), 6.57 (dd, *J* = 1.8, 7.6 Hz, 1 H, H5), 4.68 (q, *J* = 5.1 Hz, 1 H, H2′), 4.19 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.09 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 3.98 (dd, *J* = 1.8, 12.3 Hz, 1 H, H4a′), 3.72 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4b′), 3.69 (m, 1 H, H5′), 3.53 (m, 1 H, H6′), 3.24 (ddd, *J* = 2.1, 5.6, 7.6 Hz, 1 H, H3), 3.11 (ddd, *J* = 1.8, 9.7, 14.1 Hz, 1 H, H4a), 3.00 (m, 1 H, H4b), 1.33 (d, *J* = 5.3 Hz, 3 H, CH_3), 0.92 [s, 9 H, OSiC(CH_3)$_3$], 0.11, 0.10 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 151.8, 151.7 (C4″, C6″), 150.6 (C2″), 145.7 (C8″), 136.4, 128.6, 128.5, 127.8 (C_6H_5, C5″), 99.0 (C2′), 80.9 (C5), 77.7 (C6′), 71.8 (C4′), 67.7 (C3), 66.4 (C5′), 61.2 ($NCH_2C_6H_5$), 37.7 (C4), 26.0 [OSiC(CH_3)$_3$], 20.9 (CHCH_3), 18.3 [OSiC(CH_3)$_3$], –4.1, –4.3 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{26}H_{36}ClN_5O_4Si$ (546.1): C, 57.18; H 6.64; N, 12.82; Found: C, 57.44; H, 7.06; N, 12.61.

14e

$[\alpha]_D$ +24 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.78 (s, 1 H, H2″), 8.16 (s, 1 H, H8″), 7.30–7.21 (m, 5 H, C_6H_5), 6.32 (dd, *J* = 6.6, 6.7 Hz, 1 H, H5), 4.80 (q, *J* = 5.1 Hz, 1 H, H2′), 4.23 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$,), 4.11 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.10 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.93 (m, 1 H, H3), 3.84 (m, 1 H, H5′), 3.80 (m, 1 H, H4b′), 3.70 (m, 1 H, H6′), 3.38 (m, 2 H, H4a,b), 1.41 (d, *J* = 4.7 Hz, 3 H, CH_3), 0.92 [s, 9 H, OSiC(CH_3)$_3$], 0.15, 0.06 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 151.9, 151.3 (C4″. C6″), 151.0 (C2″), 146.4 (C8″), 132.4, 128.5, 128.4, 127.7 (C_6H_5, C5″), 99.2 (C2′), 86.2 (C5), 78.5 (C6′), 71.3 (C4′), 65.3 (C3), 64.9 (C5′), 62.4 ($NCH_2C_6H_5$), 35.1 (C4), 25.8 [OSiC(CH_3)$_3$], 20.9 (CHCH_3), 18.2 [OSiC(CH_3)$_3$], –4.1, –4.3 [OSi(CH_3)$_2$].

Anal. Calcd for $C_{26}H_{36}ClN_5O_4Si$ (546.1): C, 57.18; H 6.64; N, 12.82; Found: C, 57.29; H, 6.87; N, 12.72.

1-{(3*R*,5*S*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-bromopurine (13f) and 1-{(3*R*,5*R*)-2-Benzyl-3-[(2*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-bromopurine (14f)

According to the general procedure, the mixture from isoxazolidine **9** (0.66 mmol) and 6-bromopurine (0.80 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give **13f** (0.118 g, 30%) as a colorless oil and **14f** (0.063 g, 16%) as a colorless oil.

13f

$[\alpha]_D$ +95 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.98 (s, 1 H, H2″), 8.66 (s, 1 H, H8″), 7.30–7.25 (m, 5 H, C_6H_5), 6.56 (dd, *J* = 2.1, 8.0 Hz, 1 H, H5), 4.67 (q, *J* = 5.1 Hz, 1 H, H2′), 4.19 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.09 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 3.97 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.72 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4b′), 3.69 (m, 1 H, H5′), 3.53 (m, 1 H, H6′), 3.23 (ddd, *J* = 1.8, 5.6, 7.3 Hz, 1 H, H3), 3.11 (ddd, *J* = 1.8, 9.4, 14.7 Hz, 1 H, H4a), 3.02 (m, 1 H, H4b), 1.32 (d, *J* = 5.3 Hz, 3 H, CH_3), 0.92 [s, 9 H, OSiC(CH_3)$_3$], 0.11, 0.10 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 151.5, 150.2 (C4″, C6″), 145.3 (C2″), 142.4 (C8″), 136.1, 128.4, 128.3, 127.5 (C_6H_5, C5″), 98.7 (C2′), 80.7 (C5), 76.7 (C6′), 71.5 (C4′), 67.4 (C3), 66.1 (C5′), 60.9 ($NCH_2C_6H_5$), 37.4 (C4), 25.7 [OSiC(CH_3)$_3$], 20.6 (CHCH_3), 18.0 [OSiC(CH_3)$_3$], –4.3, –4.6 [OSi(CH_3)$_2$].

14f

$[\alpha]_D$ +20 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, H2″), 8.17 (s, 1 H, H8″), 7.30–7.20 (m, 5 H, C_6H_5), 6.31 (dd, *J* = 6.6, 6.7 Hz, 1 H, H5), 4.80 (q, *J* = 5.1 Hz, 1 H, H2′), 4.23 (d, *J* = 14.1 Hz, 1 H, NC$H_2C_6H_5$), 4.12 (d, *J* = 13.5 Hz, 1 H, NC$H_2C_6H_5$), 4.09 (dd, *J* = 1.2, 12.3 Hz, 1 H, H4a′), 3.93 (m, 1 H, H3), 3.84 (m, 1 H, H5′), 3.80 (dd, *J* = 1.8, 12.3 Hz, 1 H, H4b′), 3.70 (d, *J* = 1.2, 7.0 Hz, 1 H, H6′), 3.37 (m, 2 H, H4a,b), 1.40 (d, *J* = 4.7 Hz, 3 H, CH_3), 0.91 [s, 9 H, OSiC(CH_3)$_3$], 0.15, 0.05 [2 × s, 2 × 3 H, OSi(CH_3)$_2$].

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 151.8, 149.7 (C4″, C6″), 144.0 (C2″), 143.3 (C8″), 136.4, 128.5, 128.4, 127.7 (C_6H_5, C5″), 99.2 (C2′), 86.2 (C5), 78.5 (C6′), 71.3 (C4′), 65.2 (C3), 64.8 (C5′), 62.4 ($NCH_2C_6H_5$), 35.1 (C4), 25.8 [OSiC(CH_3)$_3$], 20.9 (CHCH_3), 18.2 [OSiC(CH_3)$_3$], –4.1, –4.3 [OSi(CH_3)$_2$].

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(6) *Crystal data of compound* **5**: $C_{23}H_{37}NO_6Si$, M = 451.63, orthorhombic, $P2_12_12_1$, a = 9.764 (1) Å, 10.393 (1) Å, 25.479 (2) Å, V = 2585.6 (4) Å^3, Z = 4, Dx = 1.160 mg m^{-3}, μ (Mo-Kα) = 0.126 mm^{-1}, F(000) = 976, colorless block, 0.104 × 0.146 × 0.782 mm^{-3}, 65565 diffractions measured (Rint = 0.067), 6751 unique, $wR2$ = 0.1545, conventional R = 0.0483 on I values of 2882 diffractions with $I > 2.0\sigma(I)$, $(\Delta/\sigma)_{max}$ = 0.001), S = 0.902 for all data and 280 parameters. Unit cell determination and intensity data collection (θ_{max} = 29.58°) were performed on a Gemini R diffractometer[10] at 198 (1) K. Structure solution was done busing direct methods[11] and refinements were achieved by full-matrix least-squares method[11] on F^{**2}. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 667909).

Crystal data of compound **10**: $C_{23}H_{37}NO_6Si$, M = 451.63, orthorhombic, $P2_12_12_1$, a = 11.724 (1)Å, 20.530 (2) Å, 20.887 (1) Å, V = 5027.5 (2) Å^3, Z = 8, Dx = 1.193 mg m^{-3}, μ (Mo-Kα) = 0.1246 mm^{-1}, F(000) = 1952, colorless block, 0.186 × 0.237 × 0.723 mm^{-3}, 120826 diffractions measured (Rint = 0.043), 10249 unique, $wR2$ = 0.0904, conventional R = 0.0360 on I values of 7674 diffractions with $I > 2.0\sigma(I)$, $(\Delta/\sigma)_{max}$ = 0.001), S = 1.043 for all data and 561 parameters. Unit cell determination and intensity data collection (θ_{max} = 26.37°) were performed on a Gemini R diffractometer[10] at 100 (1) K. Structure solution was done busing direct methods[11] and refinements were achieved by full-matrix least-squares method[11] on F^{**2}. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 667908).

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